FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: 427.047

U S APPLICATION NO (If known, see 37 CFR 1 5): 09/937306

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/00812	March 31, 2000	April 2, 1999

TITLE OF INVENTION: COMBINATION OF NO SYNTHASE INHIBITOR(S) AND METABOLIC ANTIOXIDANTS

APPLICANT(S) FOR DO/EO/US: AUGET et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: PCT/IB/332

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/937306	PCT/FR00/00812	427.047

21. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	$1000.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	24 - 20 =	4	x **$18.00**	$ 72.00	
Independent claims	- 3 =		x **$80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$1072.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$1072.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$1072.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$1112.00	
				Amount to be refunded:	$
				charged:	$

a. [X] A check in the amount of $ 1112.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275. A duplicate copy of this sheet is enclosed.

d. [X] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Our Ref.: 427.047

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: :
Michel AUGUET et al : PCT Date: March 31, 2000
PCT/FR00/00812 :
Serial No.: :
Filed: Concurrently Herewith :
For: COMBINATION...ANTI- :
OXIDANT(S) :
600 Third Avenue
New York, NY 10016

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

Page 1, before line 1, insert

--This application is a 371 of PCT/FR00/00812 filed March 31, 2000.--

IN THE CLAIMS:

Claim 1 (amended) A pharmaceutical composition containing, as active ingredient, at least one NO synthase inhibitory substance and at least one metabolic antioxidant substance possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable

support.

Claim 2 (amended) A pharmaceutical composition according to claim 1, containing, as active ingredient, a NO synthase inhibitory substance and a metabolic antioxidant substance.

Claim 3 (amended) A pharmaceutical composition of claim 1 wherein the NO synthase inhibitory substance and the metabolic antioxidant substance are in separated form.

Claim 4 (amended) A pharmaceutical composition of claim 1 wherein the metabolic antioxidant is selected from the group consisting of dithiothreitol, pyritinol, lipoic acid and its derivatives, the dimeric disulfide derivatives of penicillamine or N-acetylcysteine, and peptides comprising at least two cysteine residues.

Claim 5 (amended) A pharmaceutical composition of claim 1 wherein the NO synthase inhibitory substance and the metabolic antioxidant substance are in the form of a salt.

Claim 6 (amended) A pharmaceutical composition of claim 5, wherein the salt is formed from a derivative of the NO synthase inhibitory substance containing at least one basic group and a derivative of the metabolic antioxidant substance containing at least one acid group.

Claim 7 (amended) A pharmaceutical composition of claim 5 wherein the metabolic antioxidant is selected from the group consisting of lipoic acid or its derivatives, the dimeric disulfide derivatives of penicillamine or N-acetylcysteine and peptides containing at least two cysteine residues.

Claim 8 (amended) A pharmaceutical composition of claim 1 wherein the NO synthase inhibitor is selected from the group consisting of a compound of amino acid type, a compound of the guanidine isothiourea, nitro- and cyano-aryl, amino-pyridine, amino-pyrimidine, amidine, indazole and imidazole families.

Claim 9 (amended) A pharmaceutical composition of claim 8 wherein the NO synthase inhibitor of amino-acid type selected from the group consisting of is L-arginine, ornithine and lysine derivatives.

Claim 10 (amended) A pharmaceutical composition of claim 1 wherein the NO synthase inhibitor is selected from the group consisting of L-nitro-arginine, L-nitro-arginine methyl ester, L-N-monomethylarginine, aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole, 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, 2-iminotetrahydropyrimidine, N-phenyl-2-

thiophenecarboximidamine, S-ethylisothiourea, S-methyl-L-thiocitrulline and S-ethyl-L-thiocitrulline.

Claim 11 (amended) A pharmaceutical composition of claim 1 wherein the metabolic antioxidant is lipoic acid in racemic or enantiomeric form.

Claim 12 (amended) A pharmaceutical composition of claim 1 wherein the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

Cancel claims 13 to 24 and add the following claims.

--25. A method of treating pathologies in warm-blooded animals wherein nitrogen monoxide and redox status of the thiol groups are involved comprising administering to warm-blooded animals in need thereof a sufficient amount of a composition of claim 1 sufficient to treat said pathologies.

26. A method of treating a pathology selected from the group consisting of cardiovascular and cerebrovascular disorders, septic shock, radioactive irradiation, solar radiation, organ transplants, disorders of the central or peripheral nervous system and more particularly Parkinsons' disease, proliferative and inflammatory diseases, autoimmune and viral diseases, diabetes and its complications, autosomal genetic diseases and pathologies

characterized by a production or a dysfunction of nitrogen monoxide and/or involving the redox status of thiol groups in warm-blooded animals comprising administering to warm-blooded animals in need thereof a sufficient amount of a composition of claim 1 to treat said pathology.

Claim 27 (amended) The method of claim 26 wherein the pathology is selected from the group consisting of migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or hemorrhagic origin, ischemias and thromboses.

Claim 28 (amended) The method of claim 26 wherein the pathology is selected from the group consisting of migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or hemorrhagic origin, ischemias and thromboses, neurodegenerative diseases, and more particularly Parkinsons's disease, pain, cerebral or bone marrow traumas, addiction to opiates, alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders and eating disorders.

Claim 29 (amended) The method of claim 26 wherein the pathology is selected from the group consisting of migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or hemorrhagic origin, ischemias and thromboses, neurodegenerative diseases, and more particularly Parkinsons's disease, pain,

cerebral or bone marrow traumas, addiction to opiates, alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders and eating disorders, lupus, AIDS, parasitic and viral infections, diabetes and its complications including retinopathies, nephropathies and polyneuropathies, multiple sclerosis and myopathies.

Claim 30 (amended) The method of claim 26 wherein the pathology is selected from the group consisting of migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or hemorrhagic origin, ischemias and thromboses, neurodegenerative diseases, and more particularly Parkinsons's disease, pain, cerebral or bone marrow traumas, addiction to opiates, alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders and eating disorders, lupus, AIDS, parasitic and viral infections, diabetes and its complications including retinopathies, nephropathies and polyneuropathies, multiple sclerosis and myopathies, cancer, atherosclerosis, pulmonary hypertension, glomerulonephritis, portal hypertension, cataracts, psoriasis, arthrosis and rheumatoid arthritis, fibroses, amyloidoses and inflammations of the gastrointestinal system and the pulmonary system and airways.

Claim 31 (amended) The method of claim 25 wherein the NO

synthase inhibitor is selected from the group consisting of a compound of amino acid type and a compound of the guanidine, isothiourea, nitro- or cyano-aryl, amino-pyridine or amino-pyrimidine, amidine, indazole or imidazole families.

Claim 32 (amended) The method of claim 31 wherein the NO synthase inhibitor is selected from the group consisting of L-arginine, ornithine and lysine derivatives.

Claim 33 (amended) The method of claim 25 wherein NO synthase inhibitor is selected from the group consisting of L-nitro-arginine, L-nitro-arginine methyl ester, L-N-monomethylarginine, aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole, 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, 2-iminotetrahydropyrimidine, N-phenyl-2-thiophenecarboximidamine, S-ethylisothiourea, S-methyl-L-thiocitrulline and S-ethyl-L-thiocitrulline.

Claim 34 (amended) The method of claim 25 wherein the metabolic antioxidant is selected from the group consisting of dithiothreitol, pyritinol acid or its derivatives, the dimeric disulfide derivatives of penicillamine or N-acetylcysteine and peptides comprising at least two cysteine residues.

Claim 35 (amended) The method of claim 25 wherein the metabolic antioxidnt is lipoic acid, in racemic or enantiomeric form.

Claim 36 (amended) The method of claim 25 wherein the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

REMARKS

The amendment is submitted to insert reference to the PCT application and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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Enclosure: Return Receipt Postcard

COMBINATION OF NO SYNTHASE INHIBITOR(S) AND METABOLIC ANTIOXIDANT(S)

--This application is a 371 of PCT/FR00/00812 filed March 31, 2000.--

The invention relates to a pharmaceutical composition containing, as active ingredient, one or many substance(s) which interfere(s) with the synthesis of nitrogen monoxide by inhibition of NO synthase and one or many metabolic antioxidant(s) which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant(s) which intervene(s) in the redox status of thiol groups, as a combination product, in separated form, of these active ingredients.

A pharmaceutical composition and a product according to the invention are useful in the treatment of pathologies where nitrogen monoxide and the metabolism of antioxidants (such as vitamin E or glutathione) as well as the redox status of the thiol groups are involved, and in particular :

- cardiovascular and cerebrovascular disorders comprising, for example, migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or haemorragic origin, ischemias and thromboses ;

- septic shock, radioactive irradiation, solar radiation, organ transplants ;

- disorders of the central or peripheral nervous system such as, for example, neurodegenerative diseases where cerebral infarctions, senile dementia, including Alzheimer's disease, Huntington's chorea, Parkinson's disease, Creutzfeld-Jacob's disease, prion diseases, amyotrophic lateral sclerosis, but also pain, cerebral or bone marrow traumas, addiction to opiates, alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders, eating disorders (anorexia, bulimia, etc.) can be mentioned in particular ;

- proliferative and inflammatory diseases such as, for example, cancer, atherosclerosis, pulmonary hypertension, glomerulonephritis, portal hypertension, cataracts, psoriasis, arthrosis and rhumatoid arthritis, fibroses, amyloidoses, inflammations of the gastrointestinal system (colitis, Crohn's disease) or of the pulmonary system and airways (asthma, sinusitis) as well as contact or delayed hypersensitivities ;

MARKED-UP VERSION OF

CLAIMS

1. Pharmaceutical composition containing, as active ingredient, one ~~or many~~ NO synthase inhibitory substance(~~s~~) and one ~~or many~~ metabolic antioxidant substance(~~s~~) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support.

2. Pharmaceutical composition according to claim 1, containing, as active ingredient, a NO synthase inhibitory substance and a metabolic antioxidant substance.

3. Pharmaceutical composition ~~according to one~~ of claims 1 ~~to 2, characterized in~~ that the NO synthase inhibitory substance and the metabolic antioxidant substance are in separated form.

4. Pharmaceutical composition ~~according to one~~ of claims 1 ~~to 3, in which~~ the metabolic antioxidant is dithiothreitol, pyritinol, lipoic acid ~~or~~ its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, ~~or the~~ peptides comprising at least two cysteine residues.

5. Pharmaceutical composition ~~according to one~~ of claims 1 ~~to 2, characterized in~~ ~~that~~ the NO synthase inhibitory substance and the metabolic antioxidant substance are in the form of a salt.

6. Pharmaceutical composition ~~according to~~ claim 5, ~~characterized in that~~ the salt is formed from a derivative of the NO synthase inhibitory substance containing at least one basic group and a derivative of the metabolic antioxidant substance containing at least one acid group.

7. Pharmaceutical composition ~~according to one~~ of claims 5 ~~to 6, in which~~ the metabolic antioxidant is lipoic acid or its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, ~~or the~~ peptides containing at least two cysteine residues.

8. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ the NO synthase inhibitor is a compound of amino acid type ~~or~~ a compound of the guanidine, isothiourea, nitro- ~~or~~ cyano-aryl, amino-pyridine, ~~or~~ amino-pyrimidine, amidine, indazole ~~or~~ imidazole families.

9. Pharmaceutical composition ~~according to~~ of claim 8 ~~in which~~ wherein the NO synthase inhibitor of amino-acid type is L-arginine, ornithine and lysine derivatives.

selected from the group consisting of

10. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ claim 1 wherein the NO synthase inhibitor is ~~chosen from~~ L-nitro-arginine, L-nitro-arginine methyl ester, L-N-monomethylarginine, aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole, 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, 2-iminotetrahydropyrimidine, N-phenyl-2-thiophenecarboximidamide, S-ethylisothiourea, S-methyl-L-thiocitrulline and S-ethyl-L-thiocitrulline.

11. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ claim 1 wherein the metabolic antioxidant is lipoic acid in racemic or enantiomeric form.

12. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ claim 1 wherein the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

13. Product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant substance(s) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, as combination product in separated form, for simultaneous or sequential use in the treatment of pathologies in which nitrogen monoxide and the redox status of thiol groups are involved.

14. Product according to claim 13 for the treatment of pathologies such as cardiovascular and cerebrovascular disorders, septic shock, radioactive irradiation, solar radiation, organ transplants, disorders of the central or peripheral nervous system and more particularly Parkinson's disease, proliferative and inflammatory diseases, autoimmune and viral diseases, diabetes and its complications, autosomal genetic diseases and all the pathologies characterized by a production or a dysfunction of nitrogen monoxide and/or involving the redox status of thiol groups.

15. Product according to claim 14, for the treatment of cerebrovascular and cardiovascular disorders such as migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or haemorragic origin, ischemias and thromboses.

16. Product according to claim 14, for the treatment of disorders of the central or peripheral nervous system such as neurodegenerative diseases, and more particularly Parkinson's disease, pain, cerebral or bone marrow traumas, addiction to opiates,

COMBINATION OF NO SYNTHASE INHIBITOR(S) AND METABOLIC ANTIOXIDANT(S)

The invention relates to a pharmaceutical composition containing, as active ingredient, one or many substance(s) which interfere(s) with the synthesis of nitrogen monoxide by inhibition of NO synthase and one or many metabolic antioxidant(s) which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant(s) which intervene(s) in the redox status of thiol groups, as a combination product, in separated form, of these active ingredients.

A pharmaceutical composition and a product according to the invention are useful in the treatment of pathologies where nitrogen monoxide and the metabolism of antioxidants (such as vitamin E or glutathione) as well as the redox status of the thiol groups are involved, and in particular :

- cardiovascular and cerebrovascular disorders comprising, for example, migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or haemorragic origin, ischemias and thromboses ;

- septic shock, radioactive irradiation, solar radiation, organ transplants ;

- disorders of the central or peripheral nervous system such as, for example, neurodegenerative diseases where cerebral infarctions, senile dementia, including Alzheimer's disease, Huntington's chorea, Parkinson's disease, Creutzfeld-Jacob's disease, prion diseases, amyotrophic lateral sclerosis, but also pain, cerebral or bone marrow traumas, addiction to opiates, alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders, eating disorders (anorexia, bulimia, etc.) can be mentioned in particular ;

- proliferative and inflammatory diseases such as, for example, cancer, atherosclerosis, pulmonary hypertension, glomerulonephritis, portal hypertension, cataracts, psoriasis, arthrosis and rhumatoid arthritis, fibroses, amyloidoses, inflammations of the gastrointestinal system (colitis, Crohn's disease) or of the pulmonary system and airways (asthma, sinusitis) as well as contact or delayed hypersensitivities ;

. auto-immune and viral diseases such as lupus, AIDS, parasitic and viral infections, diabetes and its complications including retinopathies, nephropathies and polyneuropathies, multiple sclerosis, myopathies ;

. autosomal genetic diseases such as Unverricht-Lundborg disease ;

. pathologies characterized by a production or a dysfunction of nitrogen monoxide and/or the metabolism of glutathione and of the redox status of thiol groups.

In all these pathologies, there is experimental evidence demonstrating the involvement of nitrogen monoxide or of a dysfunction of the metabolism of glutathione (Kerwin et al., Nitric oxide : a new paradigm for second messengers, J. Med. Chem. 38, 4343-4362, 1995 ; Packer et al., Alpha-lipoic acid as biological antioxidant, Free Radical Biology & Medicine 19, 227-250, 1995). This is the case in particular in Parkinson's disease which illustrates the invention (Beal MF, Excitotoxicity and nitric oxide in Parkinson's disease pathogenesis. Ann. Neurol. 44[Suppl 1], S110-S114, 1998 ; Donato et al., Gluthathione in Parkinson's disease : a link between oxidative stress and mitochondrial damage. Ann. Neurol. 32, S111-S115, 1992). In this context, medicaments which can inhibit the formation of nitrogen monoxide and/or re-establish the biological functionality of the thiol groups or glutathione can have beneficial effects. As is shown in the experimental part, combining an NO synthase inhibitor and a metabolic antioxidant, active ingredients acting with different mechanisms, increases the therapeutic effect of these active ingredients in unexpected fashion. This invention is particularly well illustrated in an experimental pathological model of Parkinson's disease : intoxication with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine).

A subject of the invention is therefore a pharmaceutical composition containing, as active ingredient, one or many substance(s) which interfere(s) with the synthesis of nitrogen monoxide by inhibition of NO synthase and one or many metabolic antioxidant(s) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support.

A more particular subject of the invention is a pharmaceutical composition containing, as active ingredient, a substance which interferes with the synthesis of nitrogen monoxide by inhibition of NO synthase and a metabolic antioxidant which intervenes in the redox status of thiol groups.

The term NO synthase inhibitor should be understood to mean any specific or non-specific inhibitor of one of its isoforms, either constitutive (neuronal or

endothelial) or inductible (Kerwin et al., Nitric oxide: a new paradigm for second messengers, J. Med. Chem. 38, 4343-4362, 1995). NO synthase inhibitors according to the invention can be chosen, for example, from certain amino acid derivatives such as L-arginine derivatives, guanidines, isothioureas, nitro- or cyano-aryls, amino-pyridines or amino-pyrimidines, amidines, indazoles or imidazoles as defined hereafter.

The term metabolic antioxidant substance which intervenes in the redox status of thiol groups should be understood to mean any chemical substance possessing at least two thiol groups capable of forming an intra or intermolecular disulphide bridge by oxidation, this substance being able to be found in reduced or oxidized form. Such compounds allow the chelation of divalent cations, the regeneration of antioxidants such as vitamin E or glutathione, and intervene in the redox status of thiol groups. The metabolic antioxidants according to the invention can be chosen, for example, from dithiothreitol, pyritinol, lipoic acid (Packer et al., Alpha-lipoic acid as biological antioxidant, Free Radical Biology & Medicine 19, 227-250, 1995) or its derivatives as defined hereafter, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, or also the peptides containing at least two cysteine residues. These substances can be natural or synthetic.

In a pharmaceutical composition according to the invention, the NO synthase inhibitor and metabolic antioxidant can be present in separated form or in combined form forming a salt. Of course, the formation of a salt is only envisaged if one of the active ingredients has an acid group and the other active ingredient a basic group. Preferably, the salt is formed from a derivative of the NO synthase inhibitory substance containing at least one basic group and a derivative of the metabolic antioxidant containing an acid group. Thus, the NO synthase inhibitor can be chosen, for example, from the compounds as defined hereafter. The metabolic antioxidant can be chosen, for example, from lipoic acid or its derivatives as defined hereafter, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine.

A subject of the invention is also a product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant substance(s) possessing at least two thiol groups, which intervene(s) in the redox status of thiol groups, as combination product, in separated form, for simultaneous or sequential use in the treatment of pathologies in which nitrogen monoxide and/or the redox status of thiol groups are involved, such as cardiovascular and cerebrovascular disorders, septic shock, radioactive irradiation, solar radiation, organ transplants, disorders of the central or peripheral nervous system and more particularly

Parkinson's disease, proliferative and inflammatory diseases, autoimmune and viral diseases, diabetes and its complications, autosomal genetic diseases and all the pathologies characterized by a production or a dysfunction of nitrogen monoxide and/or involving the redox status of thiol groups.

In a pharmaceutical composition or product according to the invention, the NO synthase inhibitor and the metabolic antioxidant can be present in doses which can be identical or different. The doses are chosen according to the compounds combined with appropriate diluents or excipients.

The NO synthase inhibitor and metabolic antioxidant can be administered in simultaneous or sequential manner, by the same administration route or by different routes, according to whether they are present in separated or combined form. Preferably, the administration routes are oral, parenteral or topical.

Among NO synthase inhibitors, compounds of amino-acid type, non amino-acid type and aromatic amine type can be defined. NO synthase inhibitors of amino-acid type can be compounds as described in the Applications WO 95/00505, WO 94/12163, WO 96/06076, WO 98/28257, or L-arginine, ornithine, or lysine derivatives as described in the Applications WO 93/24126, WO 95/01972, WO 95/24382, WO 95/09619 and WO 95/22968 (the amino acids are excluded from this class as they have no activity in the NO system ; L-arginine alone has an activity : this is the natural substrat of NO synthase).

NO synthase inhibitors of non amino-acid type can be compounds of the guanidine, isothiourea, nitro- or cyano-aryl, amino-pyridine or amino-pyrimidine, amidine, indazole or imidazole families as well as substituted heterocycles or condensed piperidines.

NO synthase guanidine inhibitors can be compounds as defined in the Applications WO 95/28377, WO 91/04023, WO 94/21621, WO 96/18607 and WO 96/18608.

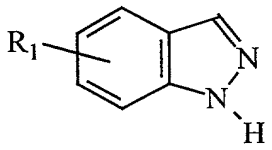
NO synthase isothiourea inhibitors can be compounds as defined in the Applications WO 95/09619, WO 96/09286, WO 94/12165, WO 96/14842, WO 96/18607, WO 96/18608, WO 96/09286, EP 717040 and EP 718294.

NO synthase nitro- or cyano-aryl inhibitors can be compounds as defined in the Application WO 94/12163.

NO synthase amino-pyridine or amino-pyrimidine inhibitors can be compounds as defined in the Applications WO 94/14780, WO 96/18616, WO 96/18617, WO 98/45294, WO 98/24766, WO 00/02860, JP 98/001470, JP 98/120654 and JP 98/036351.

NO synthase amidine inhibitors can be compounds as defined in the Applications WO 95/11014, WO 96/01817, WO 95/05363, WO 95/11231, WO 96/14844, WO 96/19440, WO 98/42696, WO 98/58934, WO 98/50380, WO 98/50382, JP 98/265450, or compounds such as N-phenyl-2-thiophenecarboximidamide.

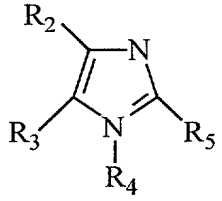
NO synthase indazole inhibitors can be compounds as defined in the Application WO 98/02442 or compounds of general formula I_A



I_A

in which R_1 represents one or more substituents chosen from a hydrogen atom, the nitro, halo, lower alkyl or lower alkoxy radical.

NO synthase imidazole inhibitors can be compounds of the general formula II_A



II_A

in which R_2 and R_3 represent, independently, a hydrogen atom, halo, hydroxy, amino, alkyl or alkoxy radical, or R_2 and R_3 are linked together and form the phenyl radical condensed with the imidazole ring, the phenyl radical being optionally substituted by one or more substituents chosen from hydroxy, trifluoromethyl, halo, carboxy, lower alkyl, lower alkoxy or lower alkenyl radicals ; R_4 represents a hydrogen atom, a lower alkyl, amino, lower alkyl amino or phenyl radical, the phenyl radical being optionally substituted by one or more substituents chosen from hydroxy, trifluoromethyl, halo, carboxy, lower alkyl, lower alkoxy or lower alkenyl radicals ; R_5 represents the hydrogen atom, a lower alkyl, amino, lower alkyl amino radical.

As it is used here, the term lower with reference to the alkyl and alkoxy groups designates saturated aliphatic hydrocarbon groups, linear or branched, containing 1 to 6 carbons such as, for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, methoxy and ethoxy. With reference to the alkenyl groups, the term lower designates groups containing 2 to 6 carbon atoms and one or more double or triple bonds such as, for example, vinyl, allyl, propenyl, isopropenyl, pentenyl, butenyl, hexanyl, propenyl and butadienyl groups. The term halo designates chloro, bromo, iodo or fluoro.

The condensed piperidines can be compounds as defined in the Application EP 870763.

The substituted heterocycles can be compounds as defined in the Applications WO 98/50372, WO 98/42667, WO 98/46611, WO 99/05131, WO 99/01455, JP 98/182618.

Preferably, the NO synthase inhibitor is a compound of amino-acid type and more particularly L-arginine, ornithine or lysine derivatives, or a compound of the guanidine, isothiourea, nitro- or cyano-aryl, amino-pyridine or amino-pyridine, amidine, indazole or imidazole families.

The metabolic antioxidant can be chosen from dithiothreitol, pyritinol, the compounds as defined in the Application EP 381439, lipoic acid (in racemic or enantiomeric form) and its derivatives, the dimeric disulphide compounds of penicillamine or N-acetylcysteine, and the peptides comprising at least two cysteine residues. Preferably, the derivatives of lipoic acid are the compounds as defined in the Applications EP 855396, EP 236929, EP 869126, FR 2707983, WO 99/45922 and JP 94227979.

A more particular subject of the invention is a composition or a product as defined above, characterized in that the NO synthase inhibitor is chosen from L-nitro-arginine (LNA), L-nitro-arginine methyl ester (LNAME), L-N-monomethylarginine (LNMMA), aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole (TRIM), 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, N-phenyl-2-thiophenecarboximidamide, 2-iminotetrahydropyrimidine, S-ethylisothiourea, S-methyl-L-thiocitrulline or S-ethyl-L-thiocitrulline.

A more particular subject of the invention is a composition or a product as defined above, characterized in that the metabolic antioxidant is lipoic acid, in racemic or enantiomeric form.

More preferably, a subject of the invention is also a composition or a product as defined above, characterised in that the NO synthase inhibitor is an inhibitor of the neuronal and/or inductible NO synthase.

NO synthase inhibitor compounds and metabolic antioxidants are commercially available or can be prepared by methods known to the person skilled in the art (or by analogy to the latter) (P. Hamley et al, Bioorganic and medicinal chemistry letters, Vol. 5 (15), 1573-1576 (1995) ; W. M. Moore et al, J. Med. Chem., 39, 669-672 (1996) ; E. P. Garvey et al., The Journal of Biological Chemistry, Vol.269 (43), 26669-26676 (1994)).

All the technical and scientific terms used in the present text have the meanings known to a person skilled in the art. Moreover, all patents (or patent applications) as well as other bibliographical references are incorporated by way of reference.

The following examples are presented to illustrate the above procedures and must in no case be considered as a limit to the scope of the invention.

EXPERIMENTAL PART :

Pharmacological study of the products of the invention

The activity of the compounds of the invention was evaluated *in vivo* on a model of neurotoxicity with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). The administration of MPTP produces a syndrome similar to Parkinson's disease resulting in a degeneration of the dopaminergic nigrostriatal neurons. This was observed in man, primates and mice [Langston JW and Ballard PA, Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, N.Engl.J.Med. 309, 310 (1983) ; Burns RS et al., A primate model of parkinsonism : selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Proc. Natl. Acad. Sci. U.S.A. 80, 4546-4550 (1983), Heikkila, RE. et al., Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6- tetrahydropyridine in mice, Science, 224, 1451-1453 (1984)].

Mice (C57BL6) weighing 15-25 g are injected three times with 15-20 mg/kg of MPTP by intraperitoneal route at 2-hour intervals. The products are injected by oral

route 90 minutes before each injection of MPTP and 90 min after the last and 24 hours after the first injection of MPTP. The mice are sacrificed 24 hours after the last injection of MPTP. The striatum is removed and its dopamine level is measured by high-performance liquid chromatography coupled with electrochemical detection. The effectiveness coefficient of the compounds is calculated according to the ratio : dopamine level of the product group + MPTP / dopamine level of the MPTP group only. A product for which the effectiveness coefficient is $\geq$ to 1.5 is considered beneficial.

Let A be the NO synthase inhibitor and B the metabolic antioxidant.

Example 1

Compound AB, combination of the active ingredients A and B. Compound A : N-phenyl-2-thiophenecarboximidamine, powerful NO synthase inhibitor. Compound B : reduced form of lipoic acid, metabolic antioxidant.

Compound of Example 1 : 4 groups of animals are constituted as follows :

Group 1 : treated with MPTP.
Group 2 : treated with A (3 mg/kg) + MPTP.
Group 3 : treated with B (10 mg/kg) + MPTP.
Group 4 : treated with AB + MPTP.

Group No.	Dopamine level ng/mg of tissue	Effectiveness coefficient
1	3.24	-
2	3.77	1.16
3	3.81	1.17
4	5.21	1.60

The results show that the lipoic acid, in reduced form, used as metabolic antioxidant at the dose of 10 mg/kg is ineffective for protecting the animal against the fall in dopamine which occurs after injection of MPTP. The N-phenyl-2-thiophenecarboximidamine used as NO synthase inhibitor at the dose of 3 mg/kg is

also ineffective. In contrast, the combination of the two compounds proves effective in restoring the dopamine level of the animals subjected to the MPTP neurotoxicity.

Example 2

Compound AB, combination of the active ingredients A and B. Compound A : N^{G}nitro-arginine, powerful inhibitor of constitutive and inductible NO synthases. Compound B : reduced form of lipoic acid, metabolic antioxidant.

Compound of Example 2 : 4 groups of animals are constituted as follows :

Group 1 : treated with MPTP.
Group 2 : treated with A (3 mg/kg) + MPTP.
Group 3 : treated with B (10 mg/kg) + MPTP.
Group 4 : treated with AB + MPTP.

Group No.	Dopamine level ng/mg of tissue	Effectiveness coefficient
1	4.11	-
2	6.98	1.69
3	4.48	1.09
4	8.65	2.1

The N^{G}nitro-arginine used as an inhibitor of NO synthases, effective at the dose of 3 mg/kg, has an increased effectiveness when it is combined with lipoic acid.

The experimental results of Examples 1 and 2 therefore show a potentializing effect, even a synergy between the two types of compounds.

CLAIMS

1. Pharmaceutical composition containing, as active ingredient, one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant substance(s) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support.

2. Pharmaceutical composition according to claim 1, containing, as active ingredient, a NO synthase inhibitory substance and a metabolic antioxidant substance.

3. Pharmaceutical composition according to one of claims 1 to 2, characterized in that the NO synthase inhibitory substance and the metabolic antioxidant substance are in separated form.

4. Pharmaceutical composition according to one of claims 1 to 3, in which the metabolic antioxidant is dithiothreitol, pyritinol, lipoic acid or its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, or the peptides comprising at least two cysteine residues.

5. Pharmaceutical composition according to one of claims 1 to 2, characterized in that the NO synthase inhibitory substance and the metabolic antioxidant substance are in the form of a salt.

6. Pharmaceutical composition according to claim 5, characterized in that the salt is formed from a derivative of the NO synthase inhibitory substance containing at least one basic group and a derivative of the metabolic antioxidant substance containing at least one acid group.

7. Pharmaceutical composition according to one of claims 5 to 6, in which the metabolic antioxidant is lipoic acid or its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, or the peptides containing at least two cysteine residues.

8. Pharmaceutical composition according to one of the preceding claims, in which the NO synthase inhibitor is a compound of amino acid type or a compound of the guanidine, isothiourea, nitro- or cyano-aryl, amino-pyridine or amino-pyrimidine, amidine, indazole or imidazole families.

9. Pharmaceutical composition according to claim 8 in which the NO synthase inhibitor of amino-acid type is L-arginine, ornithine or lysine derivatives.

10. Pharmaceutical composition according to one of the preceding claims, in which the NO synthase inhibitor is chosen from L-nitro-arginine, L-nitro-arginine methyl ester, L-N-monomethylarginine, aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole, 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, 2-iminotetrahydropyrimidine, N-phenyl-2-thiophenecarboximidamide, S-ethylisothiourea, S-methyl-L-thiocitrulline or S-ethyl-L-thiocitrulline.

11. Pharmaceutical composition according to one of the preceding claims, in which the metabolic antioxidant is lipoic acid in racemic or enantiomeric form.

12. Pharmaceutical composition according to one of the preceding claims, in which the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

13. Product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant substance(s) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, as combination product in separated form, for simultaneous or sequential use in the treatment of pathologies in which nitrogen monoxide and the redox status of thiol groups are involved.

14. Product according to claim 13 for the treatment of pathologies such as cardiovascular and cerebrovascular disorders, septic shock, radioactive irradiation, solar radiation, organ transplants, disorders of the central or peripheral nervous system and more particularly Parkinson's disease, proliferative and inflammatory diseases, autoimmune and viral diseases, diabetes and its complications, autosomal genetic diseases and all the pathologies characterized by a production or a dysfunction of nitrogen monoxide and/or involving the redox status of thiol groups.

15. Product according to claim 14, for the treatment of cerebrovascular and cardiovascular disorders such as migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or haemorragic origin, ischemias and thromboses.

16. Product according to claim 14, for the treatment of disorders of the central or peripheral nervous system such as neurodegenerative diseases, and more particularly Parkinson's disease, pain, cerebral or bone marrow traumas, addiction to opiates,

alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders, eating disorders.

17. Product according to claim 14, for the treatment of autoimmune and viral diseases such as lupus, AIDS, parasitic and viral infections, diabetes and its complications including retinopathies, nephropathies and polyneuropathies, multiple sclerosis, myopathies.

18. Product according to claim 14, for the treatment of proliferative and inflammatory diseases such as cancer, atherosclerosis, pulmonary hypertension, glomerulonephritis, portal hypertension, cataracts, psoriasis, arthrosis and rhumatoid arthritis, fibroses, amyloidoses, inflammations of the gastrointestinal system or the pulmonary system and airways.

19. Product according to one of claims 13 to 18, in which the NO synthase inhibitor is a compound of amino acid type or a compound of the guanidine, isothiourea, nitro- or cyano-aryl, amino-pyridine or amino-pyrimidine, amidine, indazole or imidazole families.

20. Product according to claim 19 in which the NO synthase inhibitor of amino-acid type is L-arginine, ornithine or lysine derivatives.

21. Product according to one of claims 13 to 20, in which the NO synthase inhibitor is chosen from L-nitro-arginine, L-nitro-arginine methyl ester, L-N-monomethylarginine, aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole, 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, 2-iminotetrahydropyrimidine, N-phenyl-2-thiophenecarboximidamide, S-ethylisothiourea, S-methyl-L-thiocitrulline or S-ethyl-L-thiocitrulline.

22. Product according to one of claims 13 to 21, in which the metabolic antioxidant is dithiothreitol, pyritinol, acid or its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, or peptides comprising at least two cysteine residues.

23. Product according to one of claims 13 to 22, in which the metabolic antioxidant is lipoic acid, in racemic or enantiomeric form.

24. Product according to one of claims 13 to 23, in which the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing OR [ ] Declaration Submitted after Initial Filing

Attorney Docket Number	
First Named Inventor	M. AUGUET
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

ASSOCIATION OF NO-SYNTHASE INHIBITOR(S) AND METABOLIC ANTIOXIDANT(S)

(Title of the invention)

the specification of which

[ ] is attached hereto

OR

[X] was filed on (MM/DD/YYYY) 03/31/2000 as United States Application Number or PCT International

Application Number PCT/FR00/00812 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
99/04134	France	04/02/1999	[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
		[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

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I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☒ Additional inventors are being named on supplemental sheet(s) attached hereto

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ADDITIONAL INVENTOR(S) Supplemental Sheet

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Inventor's Signature: Date:

Residence: City State Country Citizenship

Post Office Address:

Post Office Address:

City State Zip Country

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PRIORITY DATA (Supplemental Sheet)

Additional foreign applications:

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
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			☐	☐	☐

Additional provisional applications:

Application Number	Filing Date (MM/DD/YYYY)

Additional U.S. applications:

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

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REGISTERED PRACTITIONER INFORMATION (Supplemental Sheet)

Name	Registration Number	Name	Registration Number

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